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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,100	12/11/2000	Zhong-Ru Gan	20700-703	6340

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,100	GAN, ZHONG-RU	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-97,99,102-104,106-109,111-114,116,120-129 and 131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-97,99,102-104,106-109,111-114,116,120-129 and 131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12,20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IV (claims 78-101, 103-108, 111-113, 116-126, 128-129) drawn to a method of preparing a bioactive protein in Paper No. 22 (13 January 2003) is acknowledged. The traversal is on the ground(s) that Groups I, II, IV, and V share the same technical feature. This is found *persuasive*. Groups I, II, IV, and V are hereby rejoined and the following clams will be examined 78-97, 99, 102-104, 106-109, 111-114, 116, and 120-129 including SEQ ID NO: 1, 2, 4, and 5 as it is understood all four sequences are required to practice the Invention. Newly added claim 131 is also under consideration.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendments of Paper No. 11 (11 December 2000), Paper No. 16 (4 June 2002), and Paper No. 22 (13 January 2003) have been entered in full.

3. Claims 1-77, 98, 100, 101, 105, 110, 115, 117-119, and 130 have been cancelled. Claims 78-81, 91, and 123 have been amended. Claim 131 has been added. Claims 78-97, 99, 102-104, 106-109, 111-114, 116, 120-129, and 131 are under examination.

Information Disclosure Statement

4. The information disclosure statement filed 13 January 2003 (Paper No. 20) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because citation **AF** *EP 0 347 781 B1* is not in the English language. Reference **AF** has been placed in the application file, but the information referred to therein has not been considered as to the

merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims **78-97, 99, 102-104, 106-109, 111-114, 116, 120-122, and 131** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing a protein having a correctly folded human insulin precursor comprising expressing a recombinant protein comprising, a first peptidyl fragment, a second peptidyl fragment, and at least one cleavable peptidyl fragment linking the first and second peptidyl fragments, wherein the first peptidyl fragment is capable of increasing the yield of the bioactive conformation of an insulin precursor formed upon contract of the recombinant protein with a chaotropic auxiliary agent wherein the agent is urea, wherein the first peptidyl fragment is SEQ ID NO: 1 or SEQ ID NO: 2 (human

Growth Hormone; hGH), wherein the human insulin precursor is SEQ ID NO: 4 or SEQ ID NO: 5 does not reasonably provide enablement for a first peptidyl fragment which is at least 60% identical to SEQ ID NO: 1 or sequence variants of SEQ ID NO: 4 or SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 78-97, 99, 102-104, 106-109, 111-114, 116, 120-122, and 131 are directed to a method of producing bioactive human insulin using hGH (SEQ ID NO: 1 or SEQ ID NO: 2) as a covalently linked intramolecular chaperone and subsequent purification of the bioactive insulin produced via ultrafiltration.

7. The specification teaches that hGH can be used as a covalently linked intramolecular chaperone to improve the folding efficiency of human insulin in an *E. coli* system (Example 5 pp.23-26).

8. The art teaches that an exogenous peptide can be used as an activating peptide to improve the folding of a target polypeptide when the activating peptide has the amino acid sequence of the prosequence of the target polypeptide or of a polypeptide which has the same function as the target polypeptide and which is similar in amino acid sequence to the target polypeptide. US 5719021 (**IDS #AD**) discloses use of this method for target polypeptides such as carboxypeptidase A, carboxypeptidase B, leucine aminopeptidase, N-terminal exopeptidases, pepsin, chymotrypsinogen, thrombin, prothrombin, pancreatic elastase, cathepsins, kinin-forming and kinin destroying enzymes, streptococcal proteinase, collagenases, colstripain, and renin (claims 1-23).

9. While general guidance is given regarding the use of SEQ ID NO: 1 as the intramolecular chaperone for SEQ ID NO's 4 and 5 no working examples are presented re: viable sequence variants of SEQ ID NO: 1 with the desired bioactivity as an intramolecular chaperone.

10. Regarding a peptidyl fragment that is at least 60% identical to SEQ ID NO: 1, sequence identity is not a reliable indicator of structure and function. Due to the large quantity of experimentation necessary to identify all the applicable sequences, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable sequences, the absence of working examples directed to known sequences that are at least 60% identical to SEQ ID NO: 1, the complex nature of the invention, the unpredictability of the mutations on intramolecular chaperones [Shinde and Inouye (November 1993) "Intramolecular Chaperone Protein Folding." TIBS 18: 442-446 (**IDS #AG**)], and the breadth of the claims which fail to recite limitations for what constitutes an applicable sequence that is a least 60% identical to SEQ ID NO: 1, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

11. As noted by the Applicant in the specification, the results from the above experiment were unexpected (pp. 2, 9-10). Thus, neither the art nor the specification gives support for use of an intramolecular chaperone other than SEQ ID NO: 1 and SEQ ID NO: 2.

12. Regarding derivatives and fragments of SEQ ID NO: 1, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While

it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome

Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

13. Claims **123-129** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a first peptidyl fragment, a second peptidyl fragment comprising a human insulin precursor which exhibits insulin-like bioactivity when folded in a bioactive conformation, and at least one cleavable peptidyl fragment linking the first and second peptidyl fragments, wherein the first peptidyl fragment is SEQ ID NO: 1 (human Growth Hormone; hGH), wherein the human insulin precursor is SEQ ID NO: 4 or SEQ ID NO: 5 does not reasonably provide enablement for a first peptidyl fragment which is at least 60% identical to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims 123-129 are directed to a chimeric protein comprising

hGH (SEQ ID NO: 1 or SEQ ID NO: 2) covalently linked to a human insulin precursor protein (SEQ ID NO: 4 or SEQ ID NO: 5) via a cleavable peptidyl fragment.

14. While general guidance is given regarding a product with the claimed properties wherein the first peptidyl fragment is SEQ ID NO: 1, and the second peptidyl fragment is either SEQ ID NO: 4 or SEQ ID NO: 5, no working examples are given re: working mutants, variants, and fragments of SEQ ID NO: 1 with the same claimed bioactivity.

15. Inouye (1991) ["Intramolecular Chaperone: The Role of the Pro-Peptide in Protein Folding." Enzyme 45: 314-321 (**IDS #AH**)] teaches the mutations in the pro-peptide form of subtilisin can eliminates its activity as an intramolecular chaperone (IMC). For instance, deletion of the first 14 or 43 residues on the N-terminus of pro-subtilisin eliminated its ability to function as an IMC for subtilisin (pp. 315). Also, synthetic subtilisin pro-peptides corresponding to –44 to –77, -1 to –64, and –1 to –43 are incapable of binding subtilisin and thus can not act as IMC's (pp. 316). Also, point mutations in pro- subtilisin like Gly to Arg at position –76, Met to Thr at position –60, Lys to Glu at position –45, Asp to Asn at position 32, Val to Ala at –13 eliminate the IMC activity of pro-subtilisin (pp. 316-317; Figure 1).

16. Regarding a peptidyl fragment that is at least 60% identical to SEQ ID NO: 1, sequence identity is not a reliable indicator of structure and function. Due to the large quantity of experimentation necessary to identify all the applicable sequences, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable sequences, the absence of working examples directed to known sequences that are at least 60% identical to SEQ ID NO: 1, the complex nature of the invention, the unpredictability of the mutations on intramolecular chaperones [Shinde and

Inouye (November 1993) "Intramolecular Chaperone Protein Folding." TIBS 18: 442-446 (**IDS #AG**)], and the breadth of the claims which fail to recite limitations for what constitutes an applicable sequence that is a least 60% identical to SEQ ID NO: 1, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Regarding derivatives and fragments of SEQ ID NO: 1, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not

adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Summary

18. Claims 78-97,99,102-104,106-109,111-114,116,120-129 and 131 are rejected.

19. The following are references which are considered by the Examiner to be pertinent to the claimed invention: WO 02/079251 (10 October 2002) and US 4916212 (10 April 1990).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher James Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kennedy

CJN
March 6, 2003